

## Update Le point

Articles in the Update series give a concise, authoritative, and up-to-date survey of the present position in the selected fields, and, over a period of years, will cover many different aspects of the biomedical sciences and public health. Most of the articles will be written, by invitation, by acknowledged experts on the subject.

Les articles de la rubrique Le point fournissent un bilan concis et fiable de la situation actuelle dans le domaine considéré. Des experts couvriront ainsi successivement de nombreux aspects des sciences biomédicales et de la santé publique. La plupart de ces articles auront donc été rédigés sur demande par les spécialistes les plus autorisés.

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# The International Histological Classification of Tumours\*

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*This article reviews the development of the WHO project on the histological classification of tumours, which has included the establishment of several collaborating centres and has involved more than 300 pathologists in over 50 countries. The project has resulted in the publication, over the last 14 years, of 25 volumes in the first series of the International Histological Classification of Tumours (IHCT), each giving a classification of tumours specific to a certain site. The classifications are based primarily on the microscopic characteristics of the tumours and are concerned with morphologically identifiable cell types and histological patterns as seen by means of light microscopy and conventional staining techniques. The article also describes the relationship between IHCT and other classification and coding systems and assesses possible future developments that may result from new approaches to diagnosis.*

Communication in oncology is complicated by the large number of tumour types. Different terms are often used for the same tumour and sometimes the same term is applied to different lesions. Furthermore, the tabulation of tumours can follow a variety of formats. All of these variables hamper the comparison of data originating in different pathology laboratories.

The International Histological Classification of Tumours (IHCT) is a long-term project aimed at improving communication in oncology that was initiated by WHO over 20 years ago. Now, with the completion of the first series of 25 volumes, the present paper is intended to review the background to the classification, the methods used in developing it, the relation of the IHCT to other classifications, codes, and systems of nomenclature, and the prospects for future development.

## BACKGROUND TO THE CLASSIFICATION

The statistical tabulation of tumours has been largely based on classification by anatomical site and behaviour (malignant, benign, etc.), which has been incorporated into

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the *International classification of diseases* (ICD) since the early years of this century.

The need to be able to report data on specific histological types of tumours had been well recognized by pathologists since the 19th century, but it was not until much later that this became evident to statisticians, and then only in relation to a few particular neoplasms. Thus, in 1948, rubrics were made available in the ICD for malignant melanoma, because the behaviour of this type of tumour is different from that of other skin cancers, and for choriocarcinoma because of differences between it and other uterine cancers. The ICD classification of haematopoietic and lymphoid neoplasms is also based on cell type or histology.

The establishment of a uniform classification of tumours by histological type was greatly advanced by the publication of the *Atlas of tumor pathology*, published by the Armed Forces Institute of Pathology (USA) starting in 1949; this is a monumental series of over 50 volumes, now in its second edition. Later, in 1965, the International Union against Cancer (UICC), through its former Committee on Tumor Nomenclature, published the *Illustrated tumor nomenclature* in six languages.

The principle of statistical classification of tumours by histological type was accepted by a subcommittee of the WHO Expert Committee on Health Statistics in 1952, and in 1956 the WHO Executive Board requested the Director-General of WHO to explore the possibility of establishing centres in various parts of the world with the object of collecting human tissues and studying their histological classification. The main purpose of such centres would be to develop histological definitions of cancer types and to facilitate the wide adoption of a uniform nomenclature. This resolution was endorsed by the Tenth World Health Assembly in May 1957, and shortly afterwards a WHO Study Group on Histological Classification of Cancer Types met in Oslo to advise WHO on its implementation. The Group recommended criteria for selecting tumour sites for study and suggested the following procedure for the drafting of histological classifications and testing their validity.

For each tumour site, a tentative histological classification is drawn up by a group of experts, consisting of up to ten pathologists working in the field in question. An international centre (collaborating centre) and a number of participating laboratories are then designated by WHO to evaluate the proposed classification. These laboratories exchange histological preparations, accompanied by clinical information. The histological typing is then made in accordance with the proposed classification. Subsequently, one or more technical meetings are convened by WHO to facilitate an exchange of opinions and the classification is amended as required.

Since 1958, WHO has established collaborating centres covering tumours of the lung; breast; soft tissues; mouth; bones; ovaries; salivary glands; thyroid; skin; male urogenital tract; jaws; female genital tract; stomach and oesophagus; intestines; central nervous system; liver, biliary tract, and pancreas; upper respiratory tract; eye; and endocrine glands; as well as oral precancerous conditions, the leukaemias and lymphomas, comparative oncology, and exfoliative cytology. This work has involved more than 300 pathologists from over 50 countries.

The first book in the IHCT series was published by WHO in 1967, and the last in the first series, Volume 25, was published in 1981. Second editions of the first two publications (lung and breast tumours, respectively) are in preparation. The whole series is published in English, French, Russian, and Spanish.

The entire programme has been administered and supported by WHO, and since 1972 the National Cancer Institute, USA, through the National Research Council has made a substantial contribution to accelerate the work.

Two nongovernmental organizations collaborated with WHO in this programme: the International Council of Societies of Pathology proposed participants and distributed the

classification to national societies of pathology; and the International Academy of Pathology regularly presented the new WHO classifications at its congresses and regional meetings. The latter also provided a forum at which reports on the implementation of the classifications have been given.

## DESCRIPTION OF THE INTERNATIONAL HISTOLOGICAL CLASSIFICATION OF TUMOURS

The IHCT is composed of 25 site-specific classifications. For each site there is:

- 1) a tabular list of the categories of rubrics in the classification, with the recommended nomenclature;
- 2) a set of definitions of each tumour type with concise explanatory notes related primarily to the histological features; and
- 3) a collection of colour photomicrographs illustrating the tumour types. (These are also reproduced as a set of 35-mm transparencies that is available separately.)

The classification is based primarily on the microscopic characteristics of the tumours and is concerned with morphologically identifiable cell types and histological patterns as seen with light microscopy using conventional staining techniques.

Findings based on more sophisticated techniques such as electron microscopy, histochemistry, and immuno-localization are taken into account in the explanatory notes but are not used as a basis for classification because these techniques are not universally available.

Definitions of tumour types are generally based on descriptive histological criteria, i.e., the tissue the tumour resembles, rather than on histogenesis, i.e., the tissue from which the tumour arose. This is intended to make the definitions as reproducible as possible and not dependent on theoretical considerations regarding the cell of origin of a tumour.

In addition to benign and malignant tumours, the classification enumerates and illustrates a number of tumour-like lesions because they give rise to problems in differential diagnosis and because of the uncertain borderline between neoplasms and certain non-neoplastic lesions.

The main bases for typing and subtyping are histological characteristics. However, the justification for creating classes depends on biological differences, which may be related to the epidemiological, pathogenetic, or clinical significance of the classes. For example, cancers of the lung are divided into histological types based on different etiological associations, clinical manifestations, responses to therapy, prognoses, growth patterns, etc., in relation to morphology. Thus a histological classification of lung tumours tries to satisfy not only the pathologist, but also the surgeon, radiotherapist, chemotherapist, epidemiologist, statistician, and endocrinologist. Each may then lump tumour types into larger groups as appropriate, or simply when sample size is too small. But, in order to assure uniformity between the subtypes as well as within the larger groups, there must be clearly defined component types. The IHCT has thus tended towards splitting rather than lumping.

As the individual site-specific classifications developed, it became evident that the definitions and terminology related to certain entities common to several anatomical sites were liable to vary among the different tumour panels. This problem concerned such common entities as squamous cell carcinoma, adenocarcinoma, mucinous adenocarcinoma, anaplastic and undifferentiated carcinoma, carcinoid tumours, and carcinomas *in situ*.

In order to avoid this type of internal inconsistency, meetings of the heads of the relevant WHO centres were held. The results affected the later volumes of the series. For example, the terms "squamous cell carcinoma" and "epidermoid carcinoma" were both used in the early volumes: epidermoid carcinoma appeared in the lung and salivary gland books, whereas "squamous cell carcinoma" was the preferred term in the breast and oral classifications. Unfortunately, these two terms are interpreted differently in a number of institutions. For example, some consider squamous cell carcinoma to be more differentiated than epidermoid carcinoma and others the reverse. To promote uniformity, the heads of the WHO centres agreed to use "squamous cell carcinoma" as the preferred term, and to consider "epidermoid carcinoma" as a synonym. However, it was agreed that the definition of squamous cell carcinoma would be made separately for each site since at those locations where squamous epithelium is normally found, e.g., mouth, oesophagus, larynx, and cervix, the threshold for diagnosis is generally lower than at sites where squamous epithelium is abnormal, e.g., bladder, thyroid, breast, and lung. In the latter group, the identification of keratin or intercellular bridges is thus a requirement.

Anaplastic carcinoma and undifferentiated carcinoma are also terms that can be interpreted differently by pathologists. Most of the heads of the WHO centres felt that "undifferentiated carcinoma" best describes carcinomas showing no evidence of squamous, glandular, or other specific differentiation whereas "anaplastic carcinoma" applies best to a highly pleomorphic tumour regardless of its state of differentiation. Thus, "undifferentiated squamous cell carcinoma" would be a misnomer or at best a histogenetic guess where "anaplastic squamous cell carcinoma" could describe a pleomorphic but differentiated tumour. The term "undifferentiated" was generally preferred for tumour typing. "Anaplastic" was used in the classification of central nervous system, tumours in the sense of a tumour showing enough differentiation for cell typing but with a prominent degree of pleomorphism, hypercellularity, and loss of differentiation, e.g., anaplastic astrocytoma. The problem of using "anaplastic" and "undifferentiated" is compounded by differences in their application in other languages, e.g., in French, as compared with English.

As it was unrealistic to impose general definitions to cover all situations, each centre agreed to define tumour types as appropriate to the specific site under consideration, but keeping an overall view of how the same term was used for other sites. Furthermore, translations of terms were not to be literal, but could be adapted to common usage for the language.

## OTHER CLASSIFICATION AND CODING SCHEMES

Some confusion arises regarding the relation between the ICD, IHCT, ICD-O, SNOP, and SNOMED.

The *International histological classification of tumours* (IHCT) gives criteria for the histological definition of tumours, a recommended nomenclature, and a format for tabulation. The *International classification of diseases for oncology* (ICD-O)<sup>a</sup> is an extension of Chapter II (Neoplasms) of the 9th revision of the *International classification of diseases* (ICD-9). ICD-O provides a numerical code for neoplasms by topography, histology (morphology), and behaviour, with a separate code for histological grading and differentiation. ICD-O is thus a coded nomenclature that can be used for both topographical sites and histological types of neoplasm by those who wish to code greater detail about a neoplasm than is provided for in the neoplasms chapter of ICD-9. The

<sup>a</sup> *International classification of diseases for oncology*. Geneva, World Health Organization, 1976.

Table 1. Levels of specificity in classification and coding of neoplasms

Topography			Histology			
ICD 2 digit	ICD 3 digit	ICD 4 digit	Typing by IHCT	ICD-O SNOMED	Subtyping by IHCT	ICD-O SNOMED
<i>Cancer of:</i>	<i>Cancer of:</i>	<i>Cancer of:</i>				
Lip, oral	08	Trachea	162.0	Squamous cell carcinoma 8070/3		
Digestive organs	09	Nasal cavities	160			
		Main bronchus	162.2			
Respiratory organs	10	Larynx	161			
		Upper lobe	162.3			
		Middle lobe	162.4	Small cell carcinoma 8041/3		
Bone, skin	11	Lower lobe	162.5	Adeno- carcinoma 8140/3	Acinar	8550/3
Genitourinary organs	12	Others	162.8		Papillary	8260/3
		Unspecified	162.9		Bronchiolo- alveolar	8250/3
				Large cell carcinoma 8012/3	Solid	8230/3

*International histological classification of tumours* and the ICD-O are complementary: the former includes definitions, names, and a format for site-specific tabulation and the latter provides topography and morphology codes particularly suitable for the storage and retrieval of data.

The *Systematized nomenclature of medicine* (SNOMED),<sup>b</sup> and its predecessor the *Systematized nomenclature of pathology* (SNOP), apply the same concept of nomenclature and coding to non-neoplastic lesions as does ICD-O for tumours. The neoplasm section of ICD-O and SNOMED are identical. SNOMED also covers other fields such as etiology and function.

Because ICD-O and SNOMED are multiaxial, i.e., cover both topography and histological type, they are not primarily intended for statistical tabulation, since the potential number of rubrics is enormous. Their main application is in the storage and retrieval of data, as well as the promotion of uniform nomenclature. This latter objective is being aided by the translation of ICD-O into a number of languages, e.g. French, German, Italian, Japanese, Portuguese, Russian, and Spanish.

The relation between the ICD, ICD-O, SNOMED, and the IHCT is illustrated in Table 1 showing that five levels of specificity are available, providing users with a choice of interrelated standardized formats of progressive complexity.

### EVALUATION OF THE INTERNATIONAL HISTOLOGICAL CLASSIFICATION OF TUMOURS

The IHCT aims at uniformity, relevance, and reproducibility in order to promote international communication. Evaluation has been based primarily on measuring utilization, assessing users' modifications, and analysing criticisms.

So far the IHCT has been cited over 800 times in the medical literature: over 150 of these refer to the WHO lung tumour classification. This classification has been more widely used than the others, firstly because it was the first of the series (published in 1967) and secondly because of the frequent practice of studying lung tumours by histological type. Biological relevance plays an important role, since the histological types have distinct prognostic, etiological, and epidemiological features.

<sup>b</sup> *Systematized nomenclature of medicine*, Chicago, College of American Pathologists, 1976.

Assessment of the WHO lung tumour classification has been the object of several specific studies,<sup>c,d,e,f,g</sup> and the results of these were considered when the classification was evaluated for the second edition.

The IHCT has had important influences on other international publications. In addition to ICD-O and SNOMED, both of which use the IHCT terms for their preferred nomenclature, the *International nomenclature of diseases* (published by the Council of International Organizations of Medical Sciences) has adopted or adapted the IHCT definitions of tumour types, as well as the nomenclature. These developments represent important progress towards standardization.

## NEW APPROACHES TO DIAGNOSIS AND CLASSIFICATION

Unlike conceptual classifications, a standardized classification such as the IHCT is not meant to be changed at frequent intervals. On the other hand, the IHCT is not intended to be a static system, and it is appreciated that modifications are almost certain to be needed as experience accumulates.

Such experience can be of two sorts: new observations based on existing techniques, and observations based on new techniques. The first might question the relevance of the present categories in relation to new clinical, epidemiological, and biological correlations. For example, the division of small-cell carcinomas of the lung has already been reduced from four to three subtypes between the first and second editions of the WHO classification. It is possible that in a future revision the subtypes could be eliminated if they are found not to correlate with clinical or other phenomena. In fact, most reports based on the WHO lung tumour classification do not use the subtypes but only the main categories: epidermoid, small-cell, large-cell, and adenocarcinomas.

New observations will probably be made in the field of precancerous lesions. Several of the IHCT volumes have touched on this topic, but more data are needed before firm recommendations on standardized reporting of such lesions can be made. However, some WHO groups have already published separate reports on precancerous lesions.<sup>h,i</sup>

Malignancy grading and the correlation of degrees of differentiation and anaplasia with prognosis, are other fields in which work is needed before standards can be formulated. Such studies may help to identify subsets of patients and improve the optimal allocation of therapeutic approaches.

Despite advances in electron microscopy, histochemistry, and immunology, the diagnosis of cancer remains firmly based on light microscopy and conventional histology. From the global point of view, refinements in sophisticated techniques are less important than reaching an acceptable level of proficiency in routine diagnostic microscopy.

<sup>c</sup> HINSON, K. F. W. ET AL. An assessment of the World Health Organization classification of the histologic typing of lung tumours applied to biopsy and resected material. *Cancer*, 35: 399 (1975).

<sup>d</sup> JACQUES, J. ET AL. Appraisal of the World Health Organization classification of lung tumours. *Canadian Medical Association Journal*, 122: 897 (1980).

<sup>e</sup> LARSSON, S. & ZETTERGREN, L. Histological typing of lung cancer. Application of the World Health Organization classification to 479 cases. *Acta pathologica microbiologica scandinavica, Section A*, 84: 529 (1976).

<sup>f</sup> REINILÄ, A. & DAMMERT, K. An attempt to use the WHO typing in the histological classification of lung carcinomas. *Acta pathologica microbiologica scandinavica, Section A*, 82: 783 (1974).

<sup>g</sup> YESNER, R. ET AL. Application of the World Health Organization classification of lung carcinoma to biopsy material. *Annals of thoracic surgery*, 1: 33 (1965).

<sup>h</sup> MORSON, B. C. ET AL. Precancerous conditions and epithelial dysplasia in the stomach. *Journal of clinical pathology*, 33: 711 (1980).

<sup>i</sup> WHO COLLABORATING CENTRE FOR ORAL PRECANCEROUS LESIONS. Definition of leukoplakia and related lesions: an aid to studies on oral precancer. *Oral surgery, oral medicine, oral pathology*, 46: 518 (1978).

Electron microscopy has thrown some light on cell identification, but because of problems of expense and sampling, it has not had as much impact on tumour diagnosis as in other areas, such as renal biopsy. Electron microscopy has not helped to distinguish between benign and malignant tumours. Much of the histological classification of tumours is based on pattern recognition; electron microscopy contributes little in this respect. However, it has helped in the identification of poorly differentiated tumours by the recognition of cytoplasmic granules, such as dense-core granules and melanosomes; cytoplasmic filaments, such as keratin; and particular cellular features, such as desmosomes and the densely packed microvilli of mesothelial cells.

Immunological studies on cell functions and characteristics have given new possibilities for the diagnosis of tumours. The immunological typing of lymphoid cells has brought new information and new approaches regarding their nature, both normal and abnormal, and these studies have contributed to the revolution that has been taking place over the past 10 years in the classification of malignant lymphomas.

The identification by immuno-localization techniques of cell products, such as hormones in endocrine tumours, is a new and powerful tool that is adding an important degree of specificity to the diagnosis of tumours. Likewise, the determination of cell receptors, e.g., estrogen-binding sites, may yield important therapeutic and diagnostic information. Immuno-localization techniques therefore appear to be the most promising new avenue for development in the classification of tumours. It is unlikely that routine light microscopy will be replaced by such techniques, but it is probable that they will provide important supplementary information.

The first 20 years of the WHO IHCT project have thus resulted in the elaboration of a comprehensive approach to standardization of the histological diagnosis of tumours. Implementation and evaluation are necessary steps in the further development and refinement of this international system of communication.

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